**NCI Protocol #:** N/A

**DF/HCC Protocol #: 19-099**

**TITLE: A Phase II Randomized Double-Blind Trial of Topical Tazarotene 0.1% Gel Versus Placebo Gel for the Prevention of Regorafenib-Induced Hand-Foot-Skin Reaction**


**Coordinating Center:** Dana-Farber Cancer Institute
450 Brookline Ave
Boston, MA 02215

**Principal Investigator (PI):** Nicole LeBoeuf, MD
Dana-Farber Cancer Institute
450 Brookline Ave
nleboeuf@bwh.harvard.edu
Boston, MA

**Other Investigators:** Cecilia Larocca, MD
Marianne Tawa, NP
Ashleigh Eberly Puleo, PA-C
Nicole LeBoeuf, MD, MPH

Christine Cornejo, MD
Stephanie Liu, MD
Manisha Thakuria, MD
Lauren Guggina, MD
Jesse Hirner, MD
Cesar Virgen, MD
John Harran, RN
Zixi Liao, RN

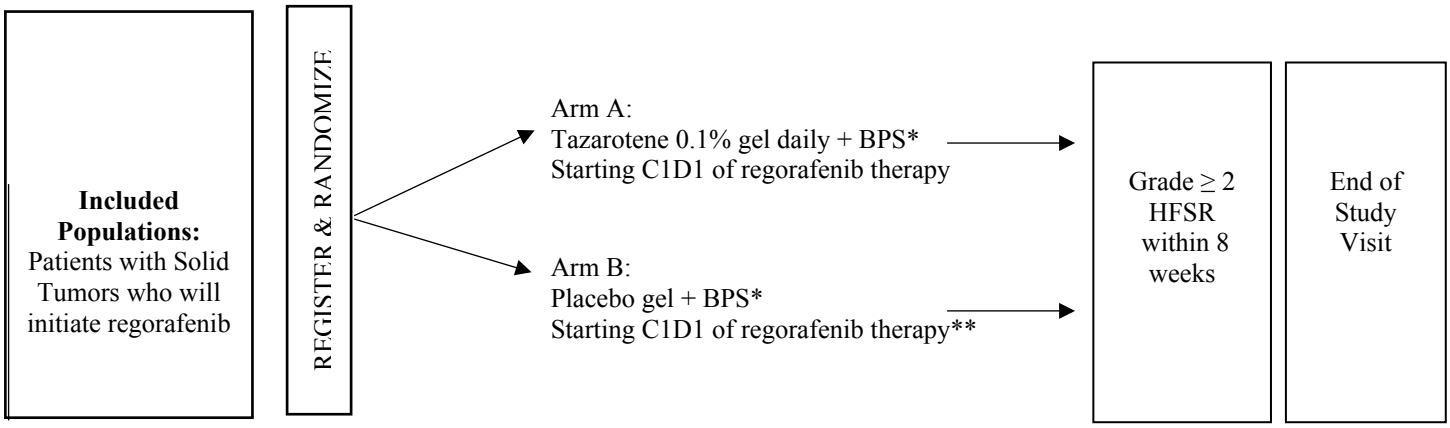
Statistician: Anita Giobbie-Hurder


**NCI-Supplied Agent(s):** *N/A*

**Study Exempt from IND Requirements per 21 CFR 312.2(b).**

**Protocol Type / Version # / Version Date:** *Version #5/22SEP2022*

SCHEMA




*Best Practice Standards (BPS) is defined as pharmacy call, DFCI approved teaching sheets and 20% urea cream recommended daily
**Cycle length corresponds to regorafenib cycle length of 28 days.

## TABLE OF CONTENTS

# 1. OBJECTIVES

## 1.1 Study Design

This is a prospective, randomized, double-blind, signal detection trial comparing placebo gel plus best practice standards (BPS) with topical tazarotene 0.1% gel plus BPS for the prevention of grade-2 or greater HFSR in patients treated with regorafenib monotherapy. BPS is defined as 20% urea cream + DFCI approved teaching sheets + pharmacy call for oral chemotherapy teaching.

## 1.2 Primary Objectives

To test the hypothesis that the preventative use of 0.1% tazarotene gel daily in addition to BPS (20% urea cream daily, with pharmacy call and DFCI approved teaching sheets) reduces the development of grade-2 or greater hand-foot skin reaction (HFSR) compared with placebo gel plus BPS.

## 1.3 Secondary Objectives

(1) To test the hypothesis that the preventative use of 0.1% tazarotene gel daily in addition to BPS:
   a. Decreases regorafenib dose modification due to HFSR
   b. Improves health-related quality of life associated with HFSR as assessed by skindex-16 survey, dermatology quality life index (DLQI) and hand-foot syndrome 14-item scale (HFS-14) prior to initiating the TKI, then at 2-4 week intervals depending on the tool
   c. Decreases global stress associated with HFSR as measured prior to initiating the TKI, then at 4 week intervals using the 10-item perceived stress scale (PSS), which has been validated in both healthy people and cancer patients.

# 2. BACKGROUND

## 2.1 Study Disease(s)

Tyrosine kinase inhibitors (TKI) are approved for the management of broad-reaching cancers that include colorectal cancer, renal cell carcinoma, gastrointestinal stromal tumors (GIST), pancreatic neuroendocrine tumor, thyroid and liver malignancies. Such targeted therapies are associated with different adverse events than their cytotoxic predecessors, with a greater frequency of side effects in the skin.

The most frequent toxicities with TKIs are dermatologic, particularly hand-foot skin reaction (HFSR) occurring in all grades in 40-85% of patients on regorafenib[1], 34% of patients on sorafenib[2] and 19% of patients on sunitinib[3]; grade 3 HFSR is reported at 13-33%[1], 9%[2] and 6%[3] for each of the drugs respectively. The incidence of HFSR of any grade from regorafenib is highest in renal cell carcinoma (71.4%) followed by GIST (60.2%), hepatocellular carcinoma (50%) and metastatic colorectal carcinoma (46.6%).[4] Grade-3 toxicity from HFSR is defined by severe skin changes that are painful and may include blisters, bleeding, edema and hyperkeratosis.[5] Grade-3 toxicities limit self-care activities of daily living (ADLs). Importantly, grade-2 HFSR, a more common event, is also associated with pain, and limits instrumental ADLs. HFSR is one of the most, if not the most, common reason for dose reduction, interruption or discontinuation of regorafenib therapy.[6,7,8,9]

HFSR has been shown to negatively impact health-related quality of life (HRQOL), more severely with higher-grade disease, as measured using the skindex-16 score, which incorporates symptom, emotion and function domains.[10]

Importantly, in the absence of evidence from prospective trials on the prevention of this toxicity, the current recommendation for patients with grade-3 toxicity is to hold the drug until severity declines. When the dose is restarted, it is done so at a lower level. With grade-2 toxicity, dose reduction is considered first line. Recommendations for supportive care are varied and based primarily on expert opinion or consensus from historical experience with similar eruptions. In the oncology literature, the focus tends to be on how best to reduce doses and reinstitute the TKI.

Given the number of malignancies treated with TKIs, the increasing numbers of TKIs in trials, the long-term duration of therapy required, the frequency of HFSR with these medications, the impact on dose and therefore potential outcomes and the impact on patient quality of life, prospectively evaluated preventative measures are imperative such that evidence based, patient-centered guidelines can be developed. Given that regorafenib has highest rates of HFSR, the drug's dose-limiting toxicity, this study aims to provide an evidenced-based approach to preventing or reducing severity of HFSR.

### 2.2 IND Agent

Tazarotene 0.1% gel is a topical retinoid that was FDA approved in 1997 for the treatment of psoriasis and acne. It is converted via rapid de-esterification to its active form ("tazarotenic acid") in humans, which binds to retinoic acid receptors (RAR). While relatively selective for RARβ, it binds all three RAR, including RARα and RARγ. In psoriasis models, tazarotene blocks epidermal proliferation as well as inflammation. This class of topical medications is thought to be overall anti-hyperproliferative and to normalize differentiation of keratinocytes.

### 2.3 Rationale

There are no clinical or molecular risk factors that have been shown to predict those patients who are predisposed to the development of HFSR. The addition of friction/trauma and heat seems to play a role. Current treatment of HFSR is based on avoiding triggers and treating hyperkeratosis with urea-based products. Urea is a keratolytic and is thought to soften and breakdown thickened skin. There are no studies or trials published to date that attempt to address the underlying pathophysiology of HFSR, rather studies to date have only tried to suppress the clinical features and symptoms.

While, the pathophysiology of HFSR is still being elucidated, there have been a multitude of studies proposing several mechanisms. Some preclinical evidence suggests that there is dysregulation in keratinocyte differentiation, leading to hyperkeratosis, pain and inflammation in the setting of tyrosine kinase inhibition. This clinically and histologically resembles palmoplantar psoriasis in many cases. These findings are supported by the histopathology of HFSR as demonstrated by acanthosis, papillomatosis, hyperkeratosis and necrosis.[11] More recently, direct keratinocyte toxicity via anion transporter, OAT6, has been implicated in HFSR in the setting of sorafenib use.[12] Additionally, several studies have implicated the inhibition of anti-angiogenic receptors such as PDGFR and VEGFR in the etiology of HFSR.[13]

Retinoids are vitamin A derivatives that act on the nuclear receptors RAR and/or RXR. These receptors are highly expressed in keratinocytes and control a variety of cellular differentiation functions. Topical tazarotene gel is FDA approved for use in psoriasis, a hyperproliferative cutaneous disorder. Psoriasis shares many clinical and histopathological features with HSFR and both are caused by keratinocyte dysregulation. Tazarotene has been shown to have anti-inflammatory properties and normalize keratinocyte differentiation. Most recently, the RAR receptor blockade, specifically with tazarotene, has been shown to locally promote angiogenesis and may address the anti-angiogenic physiology of HFSR.[14] In our experience, patients with established HFSR have responded to both topical and oral retinoids with marked improvement in symptoms.

By pre-emptively normalizing keratinocyte differentiation, decreasing inflammation associated with keratinocyte toxicity and locally promoting angiogenesis, we propose that topical retinoids, in addition to best practice standards, will diminish the incidence of HFSR, decrease dose modifications due to HFSR, decrease impact on patient quality of life and decrease global stress in those treated with regorafenib. To address our objectives, we propose a randomized signal detection trial to assess the preventative effectiveness of tazarotene plus best practices standards (BPS) compared with BPS alone.

### 2.4 Correlative Studies Background

- The primary goal of the correlative science is to begin to understand the pathways involved in the development of HFSR and, ideally, those pathways that are disrupted by our interventions
- Day 1 and 4 week (+/- 2 weeks) skin biopsies will be obtained from a cohort of 12 patients. Pre-biopsies will be taken from the lateral palm. On study biopsies will be taken from the same area in unaffected patients and from diseased areas in affected patients.
- A 4mm punch biopsy will be obtained from 12 patients (6 in each study arm); we suspect that half of patients in the control arm will develop HFSR on regorafenib and half will not. This will allow for comparison across arms and between affected and non-affected individuals to look for a signal of difference.
- Biopsies with be analyzed using standard immunohistochemistry and cyclic immunofluorescence, for the presence of activation of transcription factors known to be associated with hyper-proliferative inflammatory acquired and genetic skin disorders. Additionally, RNA transcriptional profiling will be performed to compare those patients who develop HFSR from those who do not using the nanostring platform on formalin-fixed, paraffin embedded tissue.

## 3. PARTICIPANT SELECTION

### 3.1 Eligibility Criteria

3.1.1
Participants must have histologically or cytologically confirmed solid tumors with a plan to initiate regorafenib, or having started regorafenib in the last 96 hours, via dose escalation protocol describe in the ReDOS study in CRC. The ReDOS study recommends this dose escalation of regorafenib:80mg daily x 1 week, 120mg daily x 1 week, 160mg daily times one week, off week, then 160mg daily goal, or maximum tolerated dose thereafter. This is not a separate study; this is the current standard of care for regorafenib dosing. In addition, to compare

across the cohorts, patients must be ambulatory with full use of all 4 distal extremities.

3.1.2 Age ≥ 18

3.1.3 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A)

3.1.4 Participants must have sufficient organ and marrow function in the opinion of the treating investigator. This can be based on lab reports from an outside facility.

3.1.5 Women of child-bearing potential (WOCBP) and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation

Tazarotene is known to be teratogenic, although the dose required with topical application to affect the developing human fetus is unknown. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of administration.

3.1.6 Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test.

3.1.7 Ability to understand and the willingness to sign a written informed consent document.

### 3.2 Exclusion Criteria

3.2.1 Known hypersensitivity to tazarotene

3.2.2 Regorafenib use in combination with another TKI (unless regorafenib was started in the last 96 hours.)

3.2.3 Pregnancy or non-compliance with contraception (4 weeks before, during and for at least 3 ovulatory cycles after treatment cessation). Pregnant women are excluded from this study because tazarotene is category X with the potential for teratogenic or abortifacient effects.

3.2.4 Nursing or lactating: Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with tazarotene, breastfeeding should be discontinued if the mother is treated.

3.2.5 A history of hypervitaminosis A

3.2.6 Other systemic retinoids needed for another condition (ie. Isotretinoin for inflammatory acne, acitretin for psoriasis, bexarotene for CTCL).

3.2.7 Need for treatment dose systemic steroids or systemic immunosuppressive agents (i.e., for autoimmune disease or cerebral edema) at the time of enrolment

3.2.8 Psoriasis or other autoimmune disease requiring skin directed or systemic therapy known to impact keratinocyte proliferation (UV therapy to the hands or feet, TNF inhibitors, etc).

3.2.9 Active skin disease of the hands or feet with redness, scaling or blisters prior to enrolment

3.2.10 Participants who have had any systemic chemotherapy or immunotherapy within 4 weeks prior to entering the study AND who have not recovered from adverse events on the hands and feet due to the agents administered.

3.2.11 Participants who are receiving any other investigational agents to treat HFSR.

3.2.12 Uncontrolled intercurrent illness including, but not limited to, uncontrolled lower extremity edema, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

### 3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

## 4. REGISTRATION AND RANDOMIZATION PROCEDURES

### 4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Regorafenib is not a drug that is prescribed by the Cutaneous Oncology team. This study's recruitment relies entirely on receiving referrals from other disease centers. Due to the fact that patients are referred from these outside disease centers (such as Sarcoma and GI) and that regorafenib may require insurance clearance and then mailing, we expect that screening and randomization may occur on the same day.

In an effort to increase accrual and more quickly identify potential participants that have been prescribed regorafenib in other departments within the Institute, COC will be utilizing an EPIC report to assist in the recruitment of participants. This report has been built in collaboration with pharmacy to identify patients that have been prescribed regorafenib within the last 7 days. This report can be run by the study team at any time. The COC study team may reach out to the prescribing physician to ask their permission to contact their patient directly to describe this research study and see if they would be interested in participating in this study.

The eligibility checklist(s) and all pages of the consent form(s) will be faxed to the ODQ at 617-632-2295. The ODQ will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant. ODQ will send the randomization to the research pharmacy.

Randomization can only occur during ODQ business hours (8:30am - 5pm Eastern Time, Monday through Friday excluding holidays).

An email confirmation of the registration and/or randomization will be sent to the Overall PI, study coordinator(s) from the Lead Site, treating investigator and registering person immediately following the registration and/or randomization.

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If the subject does not receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

Emergency un-blinding during the clinical trial may be required during the course of the trial to assist in the proper treatment of an AE or for regulatory reasons (e.g. for expedited safety reporting). For emergency un-blinding, the PI will need to be contacted. The PI will then send a written request (i.e. email) for an emergency un-blinding to the administrative person on call from IDS pharmacy.

### 4.2 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

## 5. TREATMENT PLAN

This is a prospective, randomized, double-blind signal detection trial comparing placebo gel plus BPS (20% urea + DFCI approved teaching sheets + pharmacy call) to tazarotene 0.1% gel plus BPS for the prevention of HFSR in patients treated with regorafenib. Each study cycle is 28 days long.

At the time of consent for regorafenib, patients will be invited to participate, consented and enrolled. Patients may already have had their first dose of regorafenib before consenting to this study, as long as regorafenib was started less than 96 hours from first application of tazarotene. Patients will be randomized 1:1 to receive either placebo gel plus best practice standards (BPS) or BPS plus tazarotene 0.1% gel daily. The current standard of care for Regorafenib includes providing patients with oral chemotherapy teaching sheets that include a Hand Skin Foot Reaction teaching sheet, pharmacy instruction and 20% urea cream daily. Participants in both arms will have urea recommended as standard best practice standards. It is available over the counter and will not be supplied.

Patients will receive regorafenib for their malignancy per their treating medical oncology team. Regorafenib is not provided as part of this study. The study team will not be making any recommendations for dose, timing of dose, concomitant medications associated with regorafenib use or prohibited foods while on regorafenib. All patients must have a plan to be treated with dose-escalation of regorafenib based on the reDOS study. The reDOS study uses this regimen: 80mg daily for week 1, 120mg daily for week 2, 160mg daily for week 3, hold drug for week 4, and then 160mg daily for each subsequent cycle with escalation and maintenance based on tolerability. All regorafenib dose adjustments are made at the discretion of the treating medical oncology team. This study team will not make any regorafenib recommendations. Treatment with tazarotene 0.1% gel or placebo is continued daily during the week that regorafenib is held.

Outcomes will be assessed by a dermatology provider at 2-week intervals until 8 weeks, then again at week 12,

16, 20, and 24. If HFSR develops, with evidence of inflammation, patients will be treated at the discretion of the treating physician in both arms of the study.
Clinical and patient demographic factors will be collected. These will include age, gender, BMI, malignancy characteristics, smoking status, occupation, hobbies, activity level, co-morbidities, marital/relationship status, ECOG performance status, prior therapies and prior dermatologic history.

Surveys listed in the study calendar will be delivered in the clinic setting. They may be given in either paper or electronic formats. Every effort will be made to collect the surveys at the required timepoints. Missing data on the questionnaires, either an incomplete or missing survey will be documented but will not be considered a protocol deviation. Survey data will be collected at the designated clinic visits+/- a 3 days window to increase our survey return response rates. Patients may complete the surveys at home, and mail them back to the study team.

The primary endpoint is the development of grade-2 or greater HFSR within 8 weeks of starting protocol therapy. This endpoint is chosen based on its significance of this toxicity grade on ADLs and dose modification. It is the endpoint time used in the reDOS study, as it allows for 2 full cycles of therapy, one with regorafenib dose escalation and one at maximum tolerated dose. It was also chosen to minimize the risk of drop out.

## 5.1 Treatment Regimen

Control arm: Pharmacy teaching call, DFCI approved teaching sheets and 20% urea applied to the palms and soles in the morning with placebo gel applied in the evening.

Intervention arm: Pharmacy teaching call, DFCI approved teaching sheets and 20% urea applied to the palms and soles in the morning + tazarotene 0.1% gel, applied to the palms and soles nightly.

Both arms will receive standard chemotherapy teaching call from pharmacy as well as the DFCI approved teaching sheets in patient education handouts. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's HFSR.

## 5.2 Pre-Treatment Criteria

### 5.2.1 Cycle 1, Day 1

N/A. There are no pretreatment criteria for this study

### 5.2.2 Subsequent Cycles

Patients will continue topical therapy as long as the regorafenib treatment plan is not discontinued permanently.

## 5.3 Agent Administration

Administration – Tazarotene 0.1% gel or placebo will be applied topically every night. Those patients experiencing < grade 2 HFSR will be allowed to continue through 24 weeks. If the endpoint of grade 2 or

greater HFSR is reached, this will be treated at the physician's discretion. Please note, with participants with large hands and feet, it is permissible to dispense two 30 gm tubes of Tazarotene 1% gel/Placebo. Earlier visits for dispensing are allowed if participants run out of drug early.

Dosing – Tazarotene 0.1% gel or placebo gel will be applied at 8 pm +/- 4 hours. Urea cream, if recommended as part of BPS will be applied at 8am +/- 4 hours.

½ Fingertip unit will be applied per palm/sole (1FTU=2% BSA). 1gram of gel covers 4% BSA. 1 palm is 1%, therefore patients will be prescribed 30g per 28-day period.

Patients will document application in a drug diary. See Appendix B.

Caregiver Precautions – Tazarotene should not be dispensed by a pregnant woman. If this is required, the caregiver should wear gloves.

Missed doses should be skipped entirely.

Please refer to Appendix E: Tazarotene or Placebo Preparation Instructions

### 5.4 General Concomitant Medication and Supportive Care Guidelines

Concomitant use of systemic retinoids, treatment dose steroids or topical steroids for HFSR prior to the development of symptoms is prohibited. Other systemic agents for the treatment of HFSR are prohibited. Topical agents beyond that outlined as best practice standards ("BPS") are prohibited.

Because there is a potential for interaction of Tazarotene with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Overall PI should be alerted if the participant is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. Appendix C presents guidelines for identifying medications/substances that could potentially interact with the study agent(s).

### 5.5 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of HFSR development, progression and tolerance of tazarotene. In the absence of treatment delays due to adverse event(s), treatment may continue for up to 24 weeks or until one of the following criteria applies:

- HFSR grade >/=2 develops and fails to respond to supportive interventions at the treating physician discretion
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the topical medication regimen

and/or documentation requirements

- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off the study, the relevant Off-Treatment/Off-Study information will be updated in OnCore.

Participants may be removed from the protocol therapy, but remain on study for the duration of the follow up period.

### 5.6 Duration of Follow Up

Participants will be followed for a minimum of 28 days (4 weeks) after removal from protocol therapy or until death, or regorafenib discontinuation with resolution of HFSR, whichever occurs first. Participants who do not develop HFSR who discontinue regorafenib do not require follow up after removal from protocol therapy. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Once removed from protocol therapy, study assessments (PE, vitals, questionnaires) will take place at visits paired with medical oncology SOC visit schedule.

### 5.7 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure Off Treatment/Off Study information is updated in OnCore in accordance with DF/HCC policy REGIST-101.

## 6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table(s).

Dose Modification Table:

| **Event** | **Management/Next Dose for *Tazarotene/Placebo*** |
|---|---|
| ≤ Grade 1 (mild irritation or peeling without pain or significant erythema on the non-palmoplantar skin) | *No change in dose* |
| Grade 2 (Erythema or irritation on the non-palmoplantar skin requiring intervention) | - Decrease frequency of application to every other day.<br>- Apply Vaseline to dorsal hands and feet prior to application of tazarotene to palms |
| Grade 3 (Erosions or bullae on the non-palmoplantar skin) | - Hold tazarotene until grade ≤ 2<br>- Apply Vaseline to dorsal hands and feet prior to application of tazarotene to palms<br>- Decrease frequency of application to two times a week. |

If drug is held, study assessments will still continue.

## 7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

### 7.1.1 Adverse Events List(s)

#### 7.1.1.1 Adverse Event List(s) for Tazarotene

Reported adverse events with tazarotene include pruritus, burning/stinging, erythema, worsening of psoriasis, irritation, skin pain, rash, desquamation, irritant contact dermatitis, skin inflammation, fissuring, bleeding and skin discoloration.

### 7.2 Adverse Event Characteristics

- **All adverse events will be graded using CTCAE v 5.0. Cutaneous AEs due to topicals will also be characterized as in the dose modification table (section 6.0 and 7.3.4). Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

### 7.3 Adverse Event Reporting

7.3.1 In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Overall PI.

7.3.2 Investigators **must** report to the Overall PI any adverse event (AE) that occurs after the initial dose of study treatment, during treatment, or within 28 days of the last dose of treatment on the local institutional SAE form.

7.3.3 DF/HCC Adverse Event Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

7.3.4 Protocol-Specific Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting to the Overall PI or the DFCI IRB. However, they still must be reported through the routine reporting mechanism (i.e. case report form).

- ≤ Grade 1 (mild irritation or peeling without pain or significant erythema on the non-palmoplantar skin)
- Grade 2 (Erythema or irritation on the non-palmoplantar skin requiring intervention)
- Any AE definitely or probably related to regorafenib

### 7.4 Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

### 7.5 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports, sentinel events or unanticipated problems that require reporting per institutional policy.

### 7.6 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

### 7.7 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. AEs will not be reported to the drug manufacturer. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions. AEs should be reported using the CTCAE v. 5.**

## 8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational administered in this study can be found in Section 7.1.

### 8.1 Tazarotene

#### 8.1.1 Description

Tazarotene is a member of the acetylenic class of retinoids and its chemical name is: Ethyl 6-[2-(4,4-dimethylthiochroman-6-yl) ethynyl] nicotinate. The molecular weight is 351.46.

Following topical application, tazarotene rapidly undergoes esterase hydrolysis to form its active metabolite, tazarotenic acid. Tazarotenic acid is highly bound to plasma proteins (>99%) and little

parent compound is found after topical application and esterification. Tazarotene and tazarotenic acid are metabolized to sulfoxides, sulfones and other polar metabolites which are eliminated through urinary and fecal pathways. The half-life of tazarotenic acid is approximately 18 hours.

8.1.2 **Form**

Tazarotene 0.1% gel is available in a collapsible aluminum tube with a tamper-evident aluminum membrane over the opening and a white polypropylene screw cap, in 15g and 30g sizes.

8.1.3 **Storage and Stability**

Store at 25 degrees C (77 degrees F), with excursions permitted between -5 and +30 degrees C (23 and 86 degrees F)

8.1.4 **Compatibility**

*N/A*

8.1.5 **Handling**

If a person other than the patient is applying the gel, gloves should be worn or hands washed following application.

8.1.6 **Availability**

Tazarotene 0.1% gel is available from various manufacturers and will be distributed by research pharmacy. Bayer will provide funding to cover the cost of the Tazarotene.

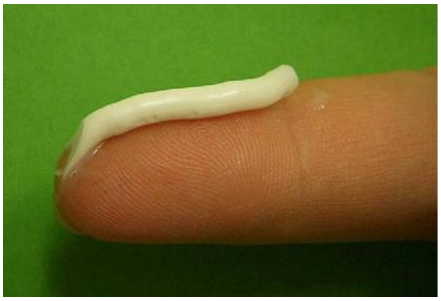
8.1.7 **Preparation**

A 30 gram tube will be supplied to the patient monthly (every 4 weeks). For participants with larger hands and feet, it is permissible to dispense two 30 gm tubes of Tazarotene 1% gel/Placebo. Earlier visits for dispensing are allowed if participants run out of drug early. Please refer to Appendix E: Tazarotene or Placebo Preparation Instructions

8.1.8 **Administration**

½ Finger tip unit will be applied per palm/sole (1FTU=2% BSA). 1gram of gel covers 4% BSA. 1 palm is 1%, therefore patients will be treated with 30g per 28 day period.

One finger tip unit (FTU) is defined as the quantity of medication dispensed from a 5mm standard nozzle from the palmar side distal index finger crease to the tip.



8.1.9 **Ordering**

The agent is commercially available and will be ordered to ensure sufficient stock before protocol activation.

8.1.10 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.11 **Destruction and Return**

Unused supply of tazarotene will be returned to pharmacy and weighed for drug accountability at the 4-week, 8 week and 12 week study visits.

## 8.2 Placebo

8.2.1 Description
Clear Wave Ultrasound Gel will be used as the placebo in this study as it closely matches the color and consistency of the active Tazarotene and is alcohol-free.

8.2.2 Form
Clear Wave Ultrasound Gel is available in 8oz tubes

8.2.3 Storage and Stability
Store at controlled room temperature
8.2.4 Compatibility
N/A

8.2.5 Handling
If a person other than the patient is applying the gel, gloves should be worn or hands washed following

application.

8.2.6 Availability
Clear Wave Ultrasound Gel is available in 8oz tubes and will be paid for by the study cost center

8.2.7 Preparation
A 30-gram tube will be supplied to the patient monthly (every 4 weeks). For participants with larger hands and feet, it is permissible to dispense two 30 gm tubes of Tazarotene 1% gel/Placebo. Earlier visits for dispensing are allowed if participants run out of drug early. Please refer to Appendix E:
Tazarotene or Placebo Preparation Instructions for study drug preparation.

8.2.8 Administration
One half finger tip unit will be applied per palm/sole (1FTU=2% BSA). 1-gram gel covers 4% BSA. 1palm is 1%, therefore patients will be treated with 30gm per 28-day period.
One finger tip unit (FTU) is defined as the quantity dispensed from a 5mm standard nozzle from the palmar side distal index finger crease to the tip.

8.2.9 Ordering
Clear Wave Ultrasound Gel is commercially available and will be ordered to ensure sufficient stock and paid for by the study cost center.

8.2.10 Accountability
The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and the disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage)

8.2.11 Destruction and Return
Unused supply of tazarotene or placebo will be returned to pharmacy and weighed for drug accountability at the 4-week, 8 week, and 12-week study visits.

## 9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Correlative studies are optional.

Patients will be asked if they would like to participate until 16 patients are identified.

- Day 1 and 4-week (+/- 2 weeks) skin biopsies will be obtained and processed in formalin fixed, paraffin embedded blocks. The pre-biopsy will be obtained from the non-dominant lateral palm. The 4-week biopsy will be obtained from the same area or an area of HFSR, if present.
- A 4mm punch biopsy will be obtained from up to 16 patients (up to 6 will be analyzed in each study arm); we suspect that half of patients in the control arm will develop HFSR on regorafenib and half will not. This will allow for comparison across arms and between affected and non-affected individuals to look for a signal of difference.

Biopsies will be analyzed using standard immunohistochemistry and cyclic immunofluorescence, for the presence of activation of transcription factors known to be associated with hyper-proliferative inflammatory acquired and genetic skin disorders.

Additionally, RNA transcriptional profiling will be performed to compare those patients who develop HFSR from those who do not using the Nanostring platform on formalin-fixed, paraffin embedded tissue. Gene sets previously developed for inflammatory skin disorders will be used.

Skin biopsy specimen collection and shipment will be paid for by Bayer Pharmaceuticals.
Left over specimens will be banked for future use.
The study team will have access to banked specimens.

### 9.1 Biomarker Studies

N/A

### 9.2 Laboratory Correlative Studies

9.2.1 Optional Correlative Skin Biopsies #1

9.2.1.1 Collection of Specimen(s): 4 mm skin punch biopsy. Skin biopsy will be placed in formalin at time of collection.

9.2.1.2 Handling of Specimens(s): Skin biopsy will be sent to the pathology core on the same day of collection to be made into a FFPE block.

Specialized Histopathology Core
Brigham and Women's Hospital
75 Francis St. Thorn 604/603b
Boston, MA 02115

FFPE blocks will be stored in the PI's office at 375 Longwood Ave, LW510 Boston, MA 02215 until all patient FFPE blocks have been obtained. At that time, they will be sent in a batch to be cut into slides.

9.2.1.3 Shipping of Specimen(s): Slides will be couriered over to the Sorger Lab for analysis once all patient biopsies have been obtained.

9.2.1.4 Site(s) Performing Correlative Study:
Sorger Lab
Peter Sorger, PhD.Harvard Medical School
200 Longwood Avenue
Warren Alpert Bldg, Room 440
Boston, MA 02115
Tel: (617) 432-6901
Peter_sorger@hms.harvard.edu
Administrative Coordinator:
Christopher Bird
Tel: (617) 432-6902
Christopher_bird.hms.harvard.edu

## 10. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 month prior to start of protocol therapy.
Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

| | | Cycle 1 | | | Cycle 2 | | Cycle 3 | Cycle 4 | Cycle 5 | Cycle 6 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pre-Study | Day 1 (Wk0) | Day 15 (Wk 2) | Day 28 (Wk 4) | Day 42 (Wk 6) | Day 56 (Wk 8) | Day 84 (Wk 12) | Day 112 (Wk 16) | Day 140 (Wk 20) | Day 168 (Wk 24) | Off Study[f] |
| | -28 days | | +/-3 days | +/-3 days | +/-3 days | +/-3 days | +/-7 days | +/-7 days | +/-7 days | +/-7 days | 28 days +/- 7 |
| *First dose of Regorafenib* | | X | | | | | | | | | |
| *First dose of Tazarotene* | | X (no more than +/- 96 hours from first Regorafenib dose) | | | | | | | | | |
| *Study Drug Dispensation: Tazarotene or placebo*[a] | X | | | X | | X | X | X | X | X | |
| *Study Drug Accountability: Tazarotene or placebo* | | | | X | | X | X | | | | |
| Informed consent | X | | | | | | | | | | |
| Demographics | X | | | | | | | | | | |
| Medical history | X | | | | | | | | | | |
| Concurrent meds | X | X---------- ----------X | | | | | | | | | |
| Physical exam | X | | X | X | X | X | X | X | X | X | X |
| Performance status | X | | | | | | | | | | X |
| Questionnaires: HFS-14, Epidemiology Questionnaire, DLQI, Skindex16, Perceived Stress Scale Assessments [b] | X | | X | X | X | X | X | X | X | X | |
| Adverse event evaluation | | X----------X | | | | | | | | | X |
| B-HCG[c] | X | | | | | | | | | | |
| Other optional correlative skin biopsies[d] | X | | | X (+/- 2 wk) | | | | | | | |
| *ODQ Randomization*[e] | X | | | | | | | | | | |

a: Tazarotene or placebo dispensation. Tazarotene will be dispensed at the pre-study visit. Tazarotene dosing starts on Day 1 along with the first dose of regorafenib. Day 1 regorafenib and tazarotene/placebo dosing could possibly occur on the same day as the pre-study visit, after the patient has been registered and randomized; this would not be considered a protocol deviation. The starting dose of regorafenib is what is considered Day 1 and all other timepoints are based on that. There is no required order for the Day 1 regorafenib and tazarotene/placebo doses. It is preferred that the patients begin their tazarotene/placebo dose on the same day as their start of regorafenib dose (on Day 1). If however for whatever reason patients begin their tazarotene/placebo dose +/- 96 hours (4 days) from their first regorafenib dose, this will not be considered a protocol deviation, but will be noted in the data.

b: Epidemiology questionnaire should be completed once at screening. All other questionnaires should be collected at the indicated timepoints. These may be collected in either paper or electronic formats.

c: Serum pregnancy test (women of childbearing potential ONLY).

d: Optional skin biopsies will be obtained from a cohort of 6 patients in each arm (first 6 patients in each arm that consent to these optional biopsies)

e: Randomization occurs after all screening assessments have been completed and the patient's eligibility has been confirmed. This could be the same day as the screening visit or anytime up to and including Day 1. ODQ will send the randomization to the research pharmacy.

f: Off-study treatment evaluation. This will occur 28 days +/- 7 days after the last regorafenib and tazorotene/placebo.

## 11. MEASUREMENT OF EFFECT

Response criteria in this study are the CTCAE toxicity criteria measuring palmo-plantar erythrodysethesia.

| CTCAE | Grade 1 | Grade 2 | Grade 3 |
|---|---|---|---|
| Palmo-plantar Erythrodysthesia | Minimal skin changes (e.g. erythema, edema or hyperkeratosis without pain | Skin changes (e.g. peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting instrumental ADLS | Severe skin changes (e.g. peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting self-care ADLS |
| | | | |

### 11.1 Antitumor Effect – Solid Tumors

N/A; tumor response is not an objective of this study.

## 12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

### 12.1 Data Reporting

12.1.1 Method

The clinical research coordinators will collect and manage the data on this study. The Office of Data Quality (ODQ) may audit this study to perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Clinical research coordinators will enter data and surveys into RedCap.

### 12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Board (DSMB) will review and monitor study progress, toxicity, safety and other data from this study. The Board is chaired by a medical oncologist from outside of DF/HCC and its membership composed of internal and external institutional representation. Information that raises any questions about participant safety or protocol performance will be addressed by the Overall PI, statistician and study team. Should any major concerns arise, the DSMB will offer recommendations regarding whether or not to suspend the study.

The DSMB will meet twice a year to review accrual, toxicity, response and reporting information. Information

to be provided to the DSMB may include: participant accrual; treatment regimen information; adverse events and serious adverse events reported by category; summary of any deaths on study; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

### 12.3 Collaborative Agreements Language

N/A. This is not a CTEP/NCI study

## 13. STATISTICAL CONSIDERATIONS

In this randomized, double-blind, signal-detection trial, patients will be randomly assigned (1:1) to tazarotene gel plus BPS or placebo gel plus BPS.

### 13.1 Study Design/Endpoints

Endpoints
The primary endpoint will be the proportion of patients in each arm who develop grade-2 or higher HFSR within the first 8 weeks of protocol therapy. A parallel secondary endpoint will be the proportion of patients in each intervention arm who develop HFSR of any grade.

Efficacy Analysis
Primary Endpoint: For each comparison, the proportion of patients with grade-2 or higher HFSR will be compared between placebo gel plus BPS and tazarotene gel plus BPS using a two-group chi-squared test. The difference between the two proportions will be summarized with a 90% confidence interval.

### 13.2 Sample Size, Accrual Rate and Study Duration

The total maximum sample size will be 70 patients (35 per arm); the minimum sample size will be 28 patients (14 per arm). The sample size for the comparison is based on a superiority design for the difference in proportions and includes one interim look for futility. We expect this study to be open to accrual for 24 months. We anticipate accruing 3 participants/month.

Based on our prior experience with BPS alone, we expect that 40-50% of patients will develop grade-2 or higher HFSR during treatment with regorafenib. The addition of tazarotene to BPS would be worthy of further study if the observed rate of HFSR is reduced to 25%. When the sample size in each arm is 35 patients, a two-group, chi-squared test with a 0.10 one-sided significance level will have 80% power to detect the difference between a proportion of 50% with HFSR using placebo gel plus BPS and 25% with tazarotene plus BPS.

An interim look for futility will be conducted after a total of 28 patients have been treated (14 with tazarotene gel plus BPS and 14 with placebo gel plus BPS; 40% information). Based on a power family beta spending function (parameter=0.3), if the chi-squared p-value at the interim look is greater than or equal to 0.458 (Z-score

> -0.107) then there will be insufficient evidence in favor of the tazarotene arm and enrollment will stop. Under this design, the probability of stopping at the time of the interim look is 0.543 if the true rate of HFSR is 50% (EaST 5.4).

Secondary comparisons will be based on the incidence of all-grade HSFR in patients treated with regorafenib. Our prior experience would suggest that the incidence of all-grade HSFR to be about 55% for patients using placebo gel plus BPS. For sample sizes of 35 patients per arm, a two-group chi-squared test with a 0.10 one-sided significance level would have 82% power when the incidence of HSFR in the intervention arm is 30%. We will also summarize the proportions of patients who develop non-HSFR adverse events that require cessation of study therapy.

---

### 13.3 Stratification Factors

There are no stratification factors.

### 13.4 Interim Monitoring Plan

An interim look for futility will be performed, as above.

### 13.5 Analysis of Primary Endpoints

Please see 13.2 Analysis of Secondary Endpoints

Additional secondary endpoints include investigation of whether tazarotene plus BPS improves health-related quality of life associated with HFSR as assessed using Skindex-16 survey, dermatology quality life index (DLQI) and hand-foot syndrome 14-item scale (HFS-14) prior to initiating the TKI, then at 2-4 week intervals depending on the tool.

Secondary endpoints also include investigation of whether the intervention decreases global stress associated with HFSR as measured prior to initiating the TKI, then at 4 week intervals using the 10-item perceived stress scale (PSS), which has been validated in both healthy people and cancer patients.

The DLQI, Skindex-16 and HFSR are validated dermatologic tools that will be administered every 2 weeks and collect findings based on the past week. The PSS is based on the prior month and will be administered every 4 weeks. The PSS is a validated measure of global stress in cancer patients.

### 13.6 Reporting and Exclusions

.

13.6.1 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first treatment. The incidence of events that are new or worsening from the time of first dose of treatment will be summarized according to system organ class and/or preferred term, severity (based on CTCAE grade), type of adverse event, and relation to study treatment. Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by primary system organ class, and type of adverse event.

13.6.2 Evaluation of the Primary Efficacy Endpoint

Data will be analyzed based on intent-to-treat.

## 14. PUBLICATION PLAN

The results of this study will be made public within 24 months of reaching the end of the study follow up period, 24 weeks after the last patient initiates therapy.

## 15. APPENDIX A PERFORMANCE STATUS CRITERIA

| ECOG Performance Status Scale | | Karnofsky Performance Scale | |
|---|---|---|---|
| Grade | Descriptions | Percent | Description |
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. | 100 | Normal, no complaints, no evidence of disease. |
| | | 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work). | 80 | Normal activity with effort; some signs or symptoms of disease. |
| | | 70 | Cares for self, unable to carry on normal activity or to do active work. |
| 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. | 60 | Requires occasional assistance, but is able to care for most of his/her needs. |
| | | 50 | Requires considerable assistance and frequent medical care. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. | 40 | Disabled, requires special care and assistance. |
| | | 30 | Severely disabled, hospitalization indicated. Death not imminent. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. | 20 | Very sick, hospitalization indicated. Death not imminent. |
| | | 10 | Moribund, fatal processes progressing rapidly. |
| 5 | Dead. | 0 | Dead. |

## 16. APPENDIX B: TAZAROTENE OR PLACEBO DRUG DIARY

19-099 Drug Diary
Participant Study ID: _____
Cycle: _____

| Urea ___%(if recommended by your oncologist) | Tazarotene or Placebo |
|---|---|
| Each morning, apply ½ fingertip to each palm & sole at 8:00 am (+/- 4 hours) | Each night, apply ½ fingertip unit (FTU) to each palm & sole at 8:00 pm (+/- 4 hours). If a dose is missed, it should be skipped entirely. |

**On the day that you start your Regorafenib dose and Tazarotene/placebo dose, please call the clinical research coordinator so that we can schedule your Day 15 appointment with us.**

_____
**Clinical Research Coordinator**
**CRC phone: _____**
**CRC email: _____**

Please indicate the date, time, amount taken and any comments in the dosing log below.

| | Date | Urea | Tazarotene or Placebo | Comments about application |
|---|---|---|---|---|
| | | Time of Daily Application | Time of daily Application | |
| Ex: | 6/1/2009 | 8:00 am | 8:00 pm | Itch on palm of left hand |
| Day 1 | | | | |
| Day 2 | | | | |
| Day 3 | | | | |
| Day 4 | | | | |
| Day 5 | | | | |
| Day 6 | | | | |
| Day 7 | | | | |
| Day 8 | | | | |
| Day 9 | | | | |
| Day 10 | | | | |
| Day 11 | | | | |
| Day 12 | | | | |
| Day 13 | | | | |
| Day 14 | | | | |
| Day 15 | | | | |
| Day 16 | | | | |
| Day 17 | | | | |
| Day 18 | | | | |
| Day 19 | | | | |
| Day 20 | | | | |
| Day 21 | | | | |
| Day 22 | | | | |
| Day 23 | | | | |
| Day 24 | | | | |
| Day 25 | | | | |
| Day 26 | | | | |
| Day 27 | | | | |
| Day 28 | | | | |

## 17. APPENDIX C: EXAMPLES OF POTENT INHIBITORS OR INDUCERS OF CYTOCHROME P450 3A4

| **Examples of potent inhibitors or inducers of cytochrome P450 3A4** | | |
|---|---|---|
| | **Potent inhibitors** | **Potent inducers** |
| CYP3A | Boceprevir<br>Cobicistat<br>Conivaptan<br>Danoprevir and ritonavir<br>Elvitegravir and ritonavir<br>Grapefruit juice<br>Indinavir and ritonavir<br>Itraconazole<br>Ketoconazole<br>Lopinavir and ritonavir<br>Paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)<br>Posaconazole<br>Ritonavir<br>Saquinavir and ritonavir<br>Telaprevir<br>Tipranavir and ritonavir<br>Troleandomycin<br>Voriconazole<br>Clarithromycin<br>Diltiazem<br>Idelalisib<br>Nefazodon<br>Nelfinavir | Carbamazepine<br>Enzalutamide<br>Mitotane<br>Phenytoin<br>Rifampin<br>St. John's wort |

Note: Strong inhibitors are drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥5-fold. Strong inducers are drugs that decreases the AUC of sensitive index substrates of a given metabolic pathway by ≥80%.
This table is prepared to provide examples of clinical inhibitors / inducers and is not intended to be an exhaustive list.
Table adapted from:
https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm
Drug-drug interactions data were collected based on a search of the University of Washington Metabolism and Transport Drug Interaction Database [Hachad et al. (2010), Hum Genomics, 5(1):61].

## 18. APPENDIX D: STUDY QUESTIONNAIRES 1-5

### HFS-14

**Specify the area affected by your hand-foot syndrome:**
☐1 Hands ☐2 Feet ☐3 Both

**Would you say your hand-foot syndrome tends to be:**
☐1 Very painful ☐2 Moderately painful ☐3 Not painful

**Please respond to the following statements as spontaneously as possible. There is no right or wrong answer, just whatever corresponds to what you experience on a daily basis.**

**1. I find it hard to turn the key in my door because of my hand-foot syndrome:**
☐1 Yes, always ☐2 Yes, from time to time ☐3 No, never

**2 I find it hard to prepare my meals because of my hand-foot syndrome:**
☐1 Yes, always ☐2 Yes, from time to time ☐3 No, never

**3 I have difficulty performing everyday actions because of my hand-foot syndrome:**
☐1 Yes, always ☐2 Yes, from time to time ☐3 No, never

**4 I have difficulty washing myself, putting on makeup (or shaving) because of my hand-foot syndrome:**
☐1 Yes, always ☐2 Yes, from time to time ☐3 No, never

**5 I find it hard to drive my car because of my hand-foot syndrome:**
☐1 Yes, always ☐2 Yes, from time to time ☐3 No, never ☐4 Not relevant to me

**6 I find it hard to put on my stockings/tights (or my socks) because of my hand-foot syndrome:**
☐1 Yes, always ☐2 Yes, from time to time ☐3 No, never

**7 I take longer than usual to get dressed because of my hand-foot syndrome:**
☐1 Yes, always ☐2 Yes, from time to time ☐3 No, never

**8 I have difficulty putting on my shoes because of my hand-foot syndrome:**
☐1 Yes, always ☐2 Yes, from time to time ☐3 No, never

**9 It is hard for me to stand because of my hand-foot syndrome:**
☐1 Yes, always ☐2 Yes, from time to time ☐3 No, never

**10 I have difficulty walking, even over quite short distances, because of my hand-foot syndrome:**
☐1 Yes, always ☐2 Yes, from time to time ☐3 No, never

**11 I tend to stay seated or lying down because of my hand-foot syndrome:**

☐1 Yes, always ☐2 Yes, from time to time ☐3 No, never

12 I find it hard to fall asleep because of my hand-foot syndrome:
☐1 Yes, always ☐2 Yes, from time to time ☐3 No, never

13 My work is suffering because of my hand-foot syndrome:
☐1 Yes, always ☐2 Yes, from time to time ☐3 No, never ☐4 Not relevant to me

14 My relationships with others are less amicable because of my hand-foot syndrome:
☐1 Yes, always ☐2 Yes, from time to time ☐3 No, never

Participant Study ID:_____
Date Survey Completed:_____
Participant Signature:_____



# EPIDEMIOLOGY QUESTIONNAIRE

## I. Patient Demographics

1. In what state did you reside when you were:
a. Born _____
b. Age 15 _____
c. Age 30 _____
d. Age 50 _____

2. Please provide your highest level of education
- ☐ Less than high school
- ☐ High school graduate
- ☐ Some or completed college
- ☐ Some or completed graduate school

3. From the choices shown, what is your race?
- ☐ Caucasian
- ☐ African-American
- ☐ Asian or Asian-American
- ☐ Other
- ☐ American Indian / Alaskan Native
- ☐ Native Hawaiian or Other Pacific
- ☐ More than one race
- ☐ Unknown or not reported

4. From the choices shown, what is your ethnicity?
- ☐ Hispanic or Latino
- ☐ Not Hispanic or Latino
- ☐ Unknown or not reported

5. From the choices shown, what is your major ancestry?
- ☐ Southern European / Mediterranean
- ☐ Scandinavian
- ☐ Celtic
- ☐ Non-Celtic
- ☐ African-American
- ☐ Hispanic, not from Spain
- ☐ Asian
- ☐ Other

9. What is your current marital status?
- ☐ Married

- ☐ Widowed
- ☐ Divorced
- ☐ Never married
- ☐ Separated

6. How much alcohol do you drink per week? _____ ounces
(1 shot = 3 ounces, 1 glass of wine = 5 ounces, or 1 can of beer = 12 ounces)

7. Have you ever smoked cigarettes?

- ☐ Never
- ☐ Prior
- ☐ Current

If you smoked in the past, when did you stop? (If you do not remember the exact date, please provide the closest estimate.) _____ (date)
If you ever smoked,
a. How many years did you smoke? _____ years
b. How many packs per day did you smoke? _____ packs per day

## II. Personal and Family History of Disease

8. Have you ever been told by a doctor or other health professional that they had PSORIASIS, ECZEMA / ATOPIC DERMATITIS, LUPUS or another skin condition?
If yes please select:
☐ Psoriasis
☐ Eczema / Atopic dermatitis
☐ Lupus

9. Have any of your close blood relatives ever been told by a doctor or other health professional that they had PSORIASIS, ECZEMA / ATOPIC DERMATITIS, LUPUS or another skin condition? By close blood relatives, we mean parents, grandparents, brothers, sisters, or natural children.

☐ (1) Yes ☐ (2) No ☐ (77) Refused ☐ (99) Don't know

If YES, please provide the following information (provide additional information on the other side of this page.)

**Relationship Condition Age at Diagnosis**

- ☐ Father
- ☐ Mother
- ☐ Grandmother
- ☐ Grandfather
- ☐ Full brother
- ☐ Half brother
- ☐ Full sister
- ☐ Half sister

- ☐ Son
- ☐ Daughter
- ☐ Psoriasis
- ☐ Eczema / Atopic dermatitis
- ☐ Lupus

10. Have you ever been told by a doctor or other health professional that you had cancer, other than the disease you are currently being treated for at DFCI?

☐(1) Yes
☐(2) No
☐(77) Refused
☐(99) Don't know

If YES, please give the following information (please add more on the back of this page if there is not enough room here):

**Type of Cancer Age at Diagnosis**

- ☐ Leukemia
- ☐ Hodgkin's Lymphoma
- ☐ Non-Hodgkin's Lymphoma
- ☐ Lung
- ☐ Breast
- ☐ Colon
- ☐ Prostate
- ☐ Brain
- ☐ Esophageal
- ☐ Renal
- ☐ Thyroid
- ☐ Unknown
- ☐ Other, please specify _____
- ☐ Leukemia
- ☐ Hodgkin's Lymphoma
- ☐ Non-Hodgkin's Lymphoma
- ☐ Lung
- ☐ Breast
- ☐ Colon
- ☐ Prostate
- ☐ Brain
- ☐ Esophageal
- ☐ Renal
- ☐ Thyroid
- ☐ Unknown
- ☐ Other, please specify _____

*Exposures*

11. Are you currently working?

☐ Yes ☐ No

If YES, what is your current occupation? Please check all that apply.

☐ (1) Management
☐ (2) Business / Financial Operations
☐ (3) Computer and Mathematical
☐ (4) Architecture / Engineering
☐ (5) Life physical and Social Science
☐ (6) Community and Social Services
☐ (7) Other
☐ (8) Education, Training and Library
☐ (9) Arts, Design, Entertainment, Sports and Media
☐ (10) Healthcare Practitioners and Technical
☐ (11) Healthcare Support
☐ (12) Protective Service
☐ (13) Food Preparation and Serving Related
☐ (14) Building and Grounds Cleaning and Maintenance
☐ (15) Personal Care and Service
☐ (16) Sales and Related Occupations
☐ (17) Office and Administrative Support
☐ (18) Farming, Fishing and Forestry
☐ (19) Construction and Extraction
☐ (20) Installation, Maintenance and Repair
☐ (21) Production
☐ (23) Transportation and Material Moving
☐ (24) Military Specific
☐ (25) Student
☐ (26) Legal
☐ (77) Refused
☐ (99) Don't know

If you are NOT currently working, please specify

☐ Retired
☐ Disabled
☐ Other, please specify _____

12. Do you currently exercise?

☐ Yes ☐ No

If yes, please describe your exercise/activity regimen

_____

13. Please describe any hobbies you participate in regularly (>2 hours per week) or for significant periods of time on occasion (ie: rock climbing, skiing, gardening, travel with significant walking, etc.)

**DERMATOLOGY LIFE QUALITY INDEX**

**DLQI**

Participant Study ID:_____
Date Survey Completed:_____
Participant Signature:_____

**The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.**

| | | | | |
|---|---|---|---|---|
| **1.** | Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been? | Very much<br>A lot<br>A little<br>Not at all | ❒<br>❒<br>❒<br>❒ | |
| **2.** | Over the last week, how **embarrassed** or **self conscious** have you been because of your skin? | Very much<br>A lot<br>A little<br>Not at all | ❒<br>❒<br>❒<br>❒ | |
| **3.** | Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**? | Very much<br>A lot<br>A little<br>Not at all | ❒<br>❒<br>❒<br>❒ | <br><br><br>Not relevant ❒ |
| **4.** | Over the last week, how much has your skin influenced the **clothes** you wear? | Very much<br>A lot<br>A little<br>Not at all | ❒<br>❒<br>❒<br>❒ | <br><br><br>Not relevant ❒ |
| **5.** | Over the last week, how much has your skin affected any **social** or **leisure** activities? | Very much<br>A lot<br>A little<br>Not at all | ❒<br>❒<br>❒<br>❒ | <br><br><br>Not relevant ❒ |
| **6.** | Over the last week, how much has your skin made it difficult for you to do any **sport**? | Very much<br>A lot<br>A little<br>Not at all | ❒<br>❒<br>❒<br>❒ | <br><br><br>Not relevant ❒ |
| **7.** | Over the last week, has your skin prevented you from **working** or **studying**? | Yes<br>No | ❒<br>❒ | <br>Not relevant ❒ |
| | If "No", over the last week how much has your skin been a problem at **work** or **studying**? | A lot<br>A little<br>Not at all | ❒<br>❒<br>❒ | |

| | | | | |
|---|---|---|---|---|
| **8.** | Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**? | Very much<br>A lot<br>A little<br>Not at all | ❒<br>❒<br>❒<br>❒ | Not relevant ❒ |
| **9.** | Over the last week, how much has your skin caused any **sexual difficulties**? | Very much<br>A lot<br>A little<br>Not at all | ❒<br>❒<br>❒<br>❒ | Not relevant ❒ |
| **10.** | Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time? | Very much<br>A lot<br>A little<br>Not at all | ❒<br>❒<br>❒<br>❒ | Not relevant ❒ |

**Please check you have answered EVERY question. Thank you.**

Participant Study ID:_____
Date Survey Completed:_____
Participant Signature:_____

# DERMATOLOGY SURVEY

This survey concerns the skin condition which has bothered you the most during the past weeks.

## THESE QUESTIONS CONCERN THE SKIN CONDITION WHICH HAS BOTHERED YOU THE MOST DURING THE PAST WEEK

| **During the past week, how often have you been bothered by:** | Never Bothered ↓ | | | • | | | Always Bothered ↓ |
|---|---|---|---|---|---|---|---|
| **1.** Your skin condition **itching** | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| **2.** Your skin condition **burning** or **stinging** | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| **3.** Your skin condition **hurting** | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| **4.** Your skin condition **being irritated** | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| **5.** The **persistence / reoccurrence** of your skin condition | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| **6.** **Worry** about your skin condition (For example: that it will spread, get worse, scar, be unpredictable, etc) | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| **7.** The **appearance** of your skin condition | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| **8.** **Frustration** about your skin condition | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| **9.** **Embarrassment** about your skin condition | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| **10.** **Being annoyed** about your skin condition | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| **11.** **Feeling depressed** about your skin condition | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| **12.** The effects of your skin condition on your **interactions with others** (For example: interactions with family, friends, close relationships, etc) | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| **13.** The effects of your skin condition on your **desire to be with people** | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| **14.** Your skin condition making it hard to **show affection** | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| **15.** The effects of your skin condition on your **daily activities** | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| **16.** Your skin condition making it hard to **work or do what you enjoy** | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |

**Have you answered every item? Yes ☐ No**

☐

Participant Study ID:_____
Date Survey Completed:_____
Participant Signature:_____



# Perceived Stress Scale

The questions in this scale ask you about your feelings and thoughts **during the last month**. In each case, you will be asked to indicate by circling *how often* you felt or thought a certain way.

Name _____ Date _____

Age _____ Gender (*Circle*): **M F** Other _____

**0 = Never 1 = Almost Never 2 = Sometimes 3 = Fairly Often 4 = Very Often**

1. In the last month, how often have you been upset because of something that happened unexpectedly?..... **0 1 2 3 4**
2. In the last month, how often have you felt that you were unable to control the important things in your life? ..... **0 1 2 3 4**
3. In the last month, how often have you felt nervous and "stressed"? ..... **0 1 2 3 4**
4. In the last month, how often have you felt confident about your ability to handle your personal problems? ..... **0 1 2 3 4**
5. In the last month, how often have you felt that things were going your way?..... **0 1 2 3 4**
6. In the last month, how often have you found that you could not cope with all the things that you had to do? ..... **0 1 2 3 4**
7. In the last month, how often have you been able to control irritations in your life?..... **0 1 2 3 4**
8. In the last month, how often have you felt that you were on top of things?.. **0 1 2 3 4**
9. In the last month, how often have you been angered because of things that were outside of your control?..... **0 1 2 3 4**
10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them? ..... **0 1 2 3 4**

**References**

The PSS Scale is reprinted with permission of the American Sociological Association, from Cohen, S., Kamarck, T., and Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior, 24,* 386-396.

Cohen, S. and Williamson, G. Perceived Stress in a Probability Sample of the United States. Spacapan, S. and Oskamp, S. (Eds.) *The Social Psychology of Health.* Newbury Park, CA: Sage, 1988.

## 19. APPENDIX E: TAZAROTENE OR PLACEBO PREPARATION INSTRUCTIONS

# DFCI # 19-099

General instructions for repackaging ID- Tazarotene 0.1% or Placebo ingredients to a new container.

Where: OPD compounding Hood ( vented to the outside)

Materials needed:

- 1 x 30g tube of active Tazarotene 0.1% or Clear wave ultrasound gel for placebo
- Chemo mat
- Spatula
- 1x Empty Aluminum tube 
- Crimpers
- Sterile wipes for cleaning the tube out of any residues.

Make sure compounding are is clean before

Wash hands and wear protective PPE ( gloves, chemo gown and a mask)

Place your chemo mat and materials

Preparation/compounding:

ACTIVE:

- Place the empty aluminum tube in upright position
- Squeeze the whole content of the original drug tube into the blank aluminum tube
- Leave about 1" empty at the bottom of the tube.
- Proceed to seal the aluminum tube

PLACEBO:

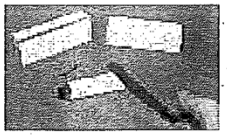
- Weight the EMPTY aluminum tube in the scale and zero out the weight.
- Place the empty aluminum tube in upright position
- Squeeze enough amount from the ultrasound gel bottle
- Leave about 1" empty at the bottom of the tube.
- Carefully place the tube in a scale- should weight approx. 25g - 30 g

Sealing the gel tube:

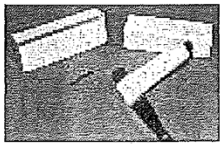
- Flatten about 1" of the bottom of the tube with a spatula.

In the next several steps, you will make 3 folds in the ointment tube.

First Fold:
Make a crease about 1/8" from the bottom of the tube with the edge of the spatula. Fold the tube completely over the spatula.

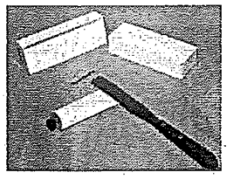


Second Fold:
With the first fold facing up, make a crease about 1/4" from the bottom of the tube.

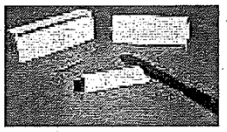


Fold the tube completely over the spatula...

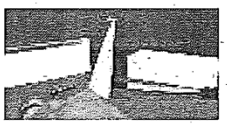
...a side view.



Third Fold:
Turn the tube over (i.e., no folds showing), and make a crease about 1/8" from the bottom of the tube. This time, do not fold the tube completely over the spatula, but only until the tube is perpendicular to the surface.



A "T" will appear in the bottom of the tube...



...a side view.

Place the metal clip on the "T"...

... and crimp with pliers or a tube crimper.

| | |
|---|---|
| Final check: | Clean up the tube for any potential left over of gel and affix appropriate label(s). |

**Video tutorial:** https://pharmlabs.unc.edu/video1.php?seal_metal_tube.flv

https://pharmlabs.unc.edu/labs/ointments/videos.htm#seal

**Cleanup:**

**Needless to say, to clean up your compounding area prior to removing your PPE**

**Labeling: Place DFCI patient label on the tube**

**Storage: Room temperature**

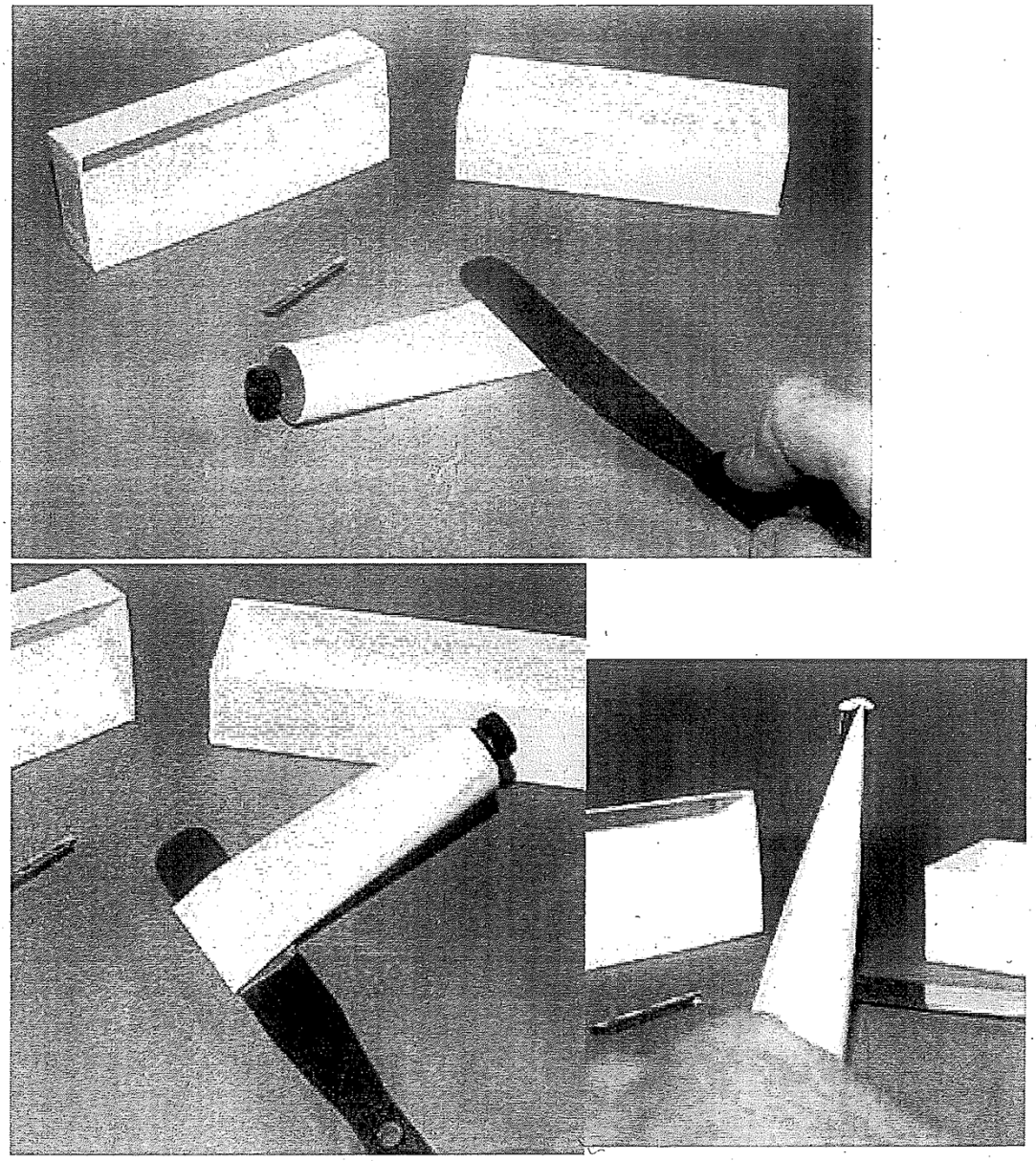
**Expiration: 30 days from re-packaging date.**

**Signing off:**

**Make sure your Active pr placebo drug has been dispensed from Velos.**

**Fill out compounding log.**

**Make sure to ask materials management to re-order more empty aluminum tubes if less than 3 are left in the original box.**



**REFERENCES**

[1] Grothey A, George S, van Cutsem E, Blay JY, Sobrero A, Demetri GD. Oncologist. Optimizing treatment outcomes with regorafenib: personalized dosing and other strategies to support patient care. 2014 Jun;19(6):669-80.
[2] Chu D, Lacouture ME, Fillos T, Wu S. Risk of hand-foot skin reaction with sorafenib: a systematic review and meta-analysis. Acta Oncol. 2008;47(2):176-86.
[3] Chu D, Lacouture ME, Weiner E, Wu S. Risk of hand-foot skin reaction with the multitargeted kinase inhibitor sunitinib in patients with renal cell and non-renal cell carcinoma: a meta-analysis. Clin Genitourin Cancer. 2009 Jan;7(1):11-9.
[4] Belum VR, Wu S, Lacouture ME. Risk of hand-foot skin reaction with the novel multikinase inhibitor regorafenib: a meta-analysis. Invest New Drugs. 2013. 31:1078-1086
[5] Gomez P, Lacouture ME. Clinical presentation and management of hand-foot skin reaction associated with sorafenib in combination with cytotoxic chemotherapy: experience in breast cancer. Oncologist. 2011;16(11):1508-19.
[6] Mross K, Frost A, Steinbild S, Hedbom S, Buchert M, Fasol U, Unger C, Kratzschmar J, Heinig R, Boix O, Christensen O. A phase I dose-escalation study of regorafenib (BAY 73–4506), an inhibitor of oncogenic, angiogenic, and stromal kinases, in patients with advanced solid tumors. Clin Cancer Res. 2012.18:2658–2667.
[7] Strumberg D, Scheulen ME, Schultheis B, Richly H, Frost A, Buchert M, Christensen O, Jeffers M, Heinig R, Boix O, Mross K. Regorafenib (BAY 73–4506) in advanced colorectal cancer: a phase I study. Br J Cancer. 2012. 106:1722–1727
[8] George S, Wang Q, Heinrich MC, Corless CL, Zhu M, Butrynski JE, Morgan JA, Wagner AJ, Choy E, Tap WD, Yap JT, Van den Abbeele AD, Manola JB, Solomon SM, Fletcher JA, von Mehren M, Demetri GD. Efficacy and safety of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of imatinib and sunitinib: a multicenter phase II trial. J Clin Oncol 2012. 30(19):2401–2407
[9] Bruix J, Tak WY, Gasbarrini A, Santoro A, Colombo M, Lim HY, Mazzaferro V, Wiest R, Reig M, Wagner A, Bolondi L. Regorafenib as second-line therapy for intermediate or advanced hepatocellular carcinoma: Multicentre, open-label, phase II safety study. Eur J Cancer. 2013. 49(16):3412–3419
[10] Nardone B, Hensley JR, Kulik L, West DP, Mulcahy M, Rademaker A, Lacouture ME. The effect of hand-foot skin reaction associated with the multikinase inhibitors sorafenib and sunitinib on health-related quality of life. J Drugs Dermatol. 2012 Nov;11(11):e61-5.
[11] Yang CH, Lin WC, Chuang CK, Chang YC, Pang ST, Lin YC, et al. Hand-foot skin reaction in patients treated with sorafenib: a clinicopathological study of cutaneous manifestations due to multitargeted kinase inhibitor therapy. Br J Dermatol. 2008;158(3):592–6.
[12] Zimmerman EI, Gibson AA, Hu S, Vasilyeva A, Orwick SJ, Du G, et al. Multikinase inhibitors induce cutaneous toxicity through OAT6-mediated uptake and MAP3K7-driven cell death. Cancer Res. 2016;76(1):117–26
[13] Kumutnart Chanprapaph, Suthinee Rutnin, Vasanop Vachiramon. Multikinase Inhibitor-Induced Hand–Foot Skin Reaction: A Review of Clinical Presentation, Pathogenesis, and Management. Am J Clin Dermatol (2016) 17:387–402.
[14] Zen AA, Nawrot DA, Howarth A, Caporali A, Ebner D, Vernet A, Schneider JE, Bhattacharya S. The retinoid agonist Tazarotene promotes angiogenesis and wound healing. Mol Ther. 2016 Aug 2. doi: 10.1038/mt.2016.153. [Epub ahead of print]